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CH DE FR GB LI(71) Applicant: **ZYMARK CORPORATION**
Zymark Center,
68 Elm Street
Hopkinton
Massachusetts 01748 (US)

(72) Inventor: **Hutchins, Burleigh M.**
28 Briar Drive
Milford, MA 01757 (US)
Inventor: **Rubinstein, Randall B.**
255 Mansfield Street
Sharon, MA 02067 (US)
Inventor: **Hixon, Barry T.**
118 Cottage Street
Franklin, MA 02038 (US)
Inventor: **Buote, William J.**
17 Lamplight Circle
Natick, MA 01760 (US)

(74) Representative: **Thomson, Paul Anthony et al**
Potts, Kerr & Co.
15, Hamilton Square
Birkenhead
Merseyside L41 6BR (GB)

(54) **Automatic dissolution testing system.**

(57) A dissolution testing system including a base (26); a plurality of vessels (31) mounted on the base; an agitation mechanism (33-35) for agitating a liquid content (32) of the vessels; and a head (38) supported above each of the vessels and operable to automatically inject a liquid media into the vessel.

Retained by the control head (38) is a spray wash tube (39) connected to the spray wash line (16), a media fill tube (41) connected to the fill line (19), an aspiration probe (42) connected to the aspirate line (18), a sampling probe (43) connected to the sampling line (17), a pH adjustment and media replacement tube (44) connected to a pH adjustment

and media replacement line (45) and a temperature detector (46). Also retained by the control head (38) is an aspiration probe drive mechanism (48), a sample probe drive mechanism (49) (Fig.3), a stepping motor (51) (Fig.4) and an interconnect board (52). Connected to the interconnect board (52) is a cable connector (53) that receives a plug (54) (Fig.5) on the electrical cable (21). The head is covered by a cover (50).

A sample tablet dispenser (57) is mounted on the control head (38) and is coupled to the stepping motor (51).

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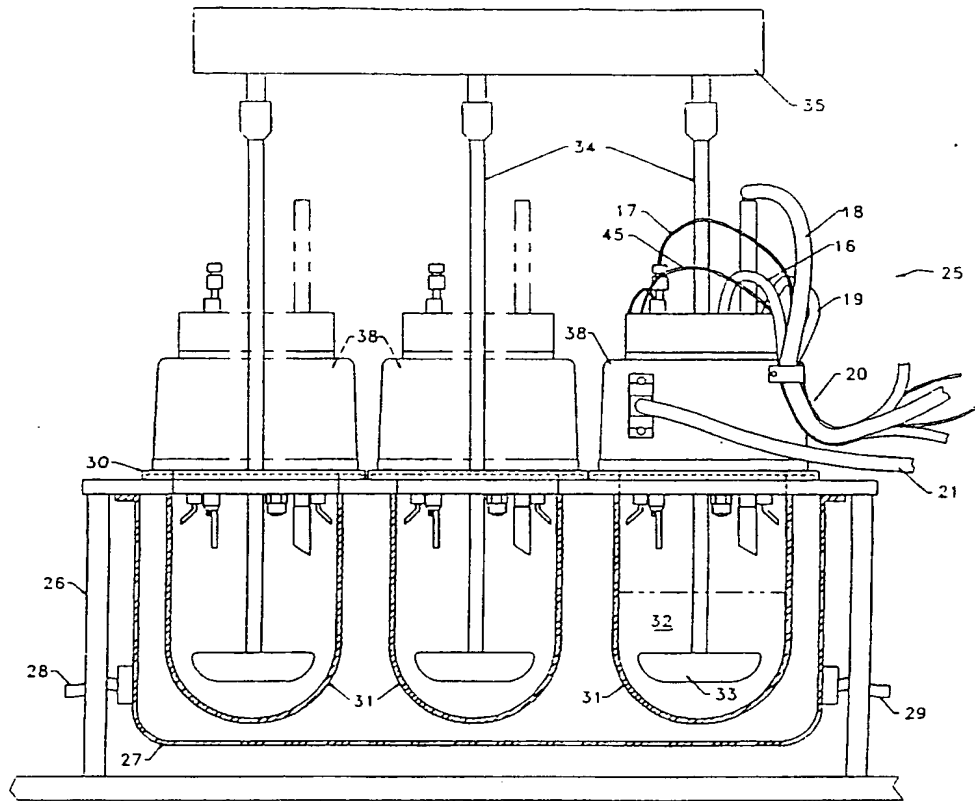


FIG. 2

BACKGROUND OF THE INVENTION

In pharmaceutical laboratories, dissolution testing is playing an increasingly important role. Such testing determines the amount of active substance in a pharmaceutical formulation unit given off to a defined medium within a defined period of time. The active substance is generally contained in a pharmaceutical dosage form such as a capsule, tablet, coated tablet or the like, which is used as a therapeutic agent. Typically, a dissolution test is run in a vessel that contains a known volume of media which is usually DI water kept at a temperature of 37C. The active substance is dropped into the vessel of media and a paddle is spun to gently agitate the media. Samples are removed periodically and injected into analyzer equipment such as UV cells, fraction collectors or HPLC systems. After completion of a test cycle, the vessels are thoroughly washed before initiation of a subsequent cycle. Because most of the operational procedures are performed manually, current dissolution testing is highly labor intensive.

The object of this invention, therefore, is to provide an improved dissolution testing system that more efficiently performs desired test procedures.

SUMMARY OF THE INVENTION

The invention is a dissolution testing system including a base; a plurality of vessels mounted on the base; an agitation mechanism for agitating a liquid content of the vessels; and a head supported above each of the vessels and operable to automatically inject a liquid media into the vessel. The provision of heads that automatically inject liquid into each test vessel significantly reduces the labor requirements of a test cycle.

According to one feature of the invention, the head further includes a spray nozzle for introducing a cleaning liquid into the vessel. Automatic washing further reduces the labor intensiveness of the process.

According to other features of the invention, each head includes a fill nozzle disposed to direct the liquid media into the vessel, fill tubing providing communication between the fill nozzle and a source of liquid media, and wash tubing providing communication between the spray nozzle and a source of cleaning liquid. The wash and fill tubings facilitate the introduction of liquid media and cleaning liquid into the vessel.

According to yet another feature of the invention, each head further includes an adjustment nozzle for injecting a pH adjustment solution into the vessel. Additional labor savings are provided by the adjustment mechanism.

According to further features of the invention, the fill and adjustment nozzles are disposed, respectively, to direct the source of liquid media and the adjustment solution against a sidewall portion of the vessel. Undesirable splashing of liquid is reduced by the transversely oriented nozzles.

According to yet additional features of the invention, each head further includes a sampling mechanism for withdrawing a liquid sample from the vessel, and an aspiration mechanism for removing the liquid content of the vessel. Additional labor savings are promoted by the sampling and aspiration mechanisms.

According to still other features of the invention, the sampling mechanism includes a sampling probe for withdrawing the liquid sample and a sampling drive for moving the sampling probe into and out of the vessel; and the aspiration mechanism includes an aspiration probe for removing the liquid content and an aspiration drive for moving the aspiration probe into and out of the vessel. These features facilitate desired sample removal and aspiration of the vessels.

According to yet another feature of the invention, each head further includes a detector for detecting the temperature of a liquid content of the vessel. Controlled dissolution testing is enhanced by the temperature detector.

According to a further feature of the invention, each head includes a dispenser for automatically dispensing a solid sample into the vessel. Automatic dispensing of solid samples further reduces the manual labor requirements of the system.

The invention also encompasses a method of dissolution testing in a system including a base, a plurality of vessels mounted on the base, and an agitation mechanism for agitating a liquid content of the vessels; the method including the steps of automatically filling each of the vessels with a media liquid; withdrawing liquid samples from each of the vessels; and simultaneously removing the liquid content of all the vessels. The method significantly reduces the labor requirements of dissolution testing by eliminating manual steps.

According to further features, the above method includes the steps of sequentially injecting a pH adjustment solution into the vessels, and sequentially injecting doses of replacement liquid media into the vessels. Further labor savings are provided by these features.

The invention additionally encompasses a method of dissolution testing in a system including a base, a plurality of vessels mounted on the base, and an agitation mechanism for agitating a liquid content of the vessels; the method including the steps of filling the vessels with liquid media; withdrawing a liquid sample from each vessel; removing the liquid content from each vessel; washing

each vessel with a cleaning liquid; spraying each vessel with liquid media; and removing the cleaning liquid and liquid media solution from each vessel. The method prevents the undesirable dilution of subsequent test samples with cleaning liquid.

DESCRIPTION OF THE DRAWINGS

These and other objects and features of the invention will become more apparent upon a perusal of the following description taken in conjunction with the accompanying drawings wherein:

Fig. 1 is a front view of a control unit for the dissolution testing system of the invention;

Fig. 2 is a front view, partially in cross section, of a test assembly for the system;

Fig. 3 is a rear view, partially in cross section, of a control head shown in Fig. 2;

Fig. 4 is a front view, partially in cross section of the control head shown in Fig. 3;

Fig. 5 is a left side view, partially in cross section of the control head shown in Figs. 3 and 4; and

Fig. 6 is a schematic diagram of a dissolution testing system according to the invention.

DESCRIPTION OF THE INVENTION

A control unit 11 (Fig. 1) includes a cabinet 12 retaining a plurality of fluid pumps 13, a liquid filter holding mechanism 14 and a dispenser mechanism 15 for dispensing filters into the filter holding mechanism 14. Extending out of the cabinet 12 are a plurality of sets 20 of lines, only one set being shown. Each set 20 includes a spray wash line 16, a sampling line 17, a waste aspirate line 18, a media fill line 19 and electrical cable 21. An output coupling 22 is provided for transmitting test samples to analyzer equipment. Other components retained within the cabinet 12 are illustrated in Fig. 6.

A test assembly 25 (Fig. 2) includes a rack base 26 that supports a liquid reservoir 27 having an inlet 28 and an outlet 29 for circulating heating water. Also mounted on the rack base 26 and extending into the liquid reservoir 27 so as to be heated thereby are six two dimensionally aligned open upper ended vessels 31, only three of which are shown. Each of the vessels 31 receives a quantity of liquid media 32 that is heated by water in the reservoir 27. The liquid media 32 in each vessel 31 is agitated by a paddle 33 rotated by a shaft 34 driven by a paddle drive assembly 35. Mounted over each of the vessels 31 on a base plate 30 is a control head 38, only one of which is shown in detail. Liquid communication between the control unit 11 and each of the control heads 38 is provided by one of the line sets 20 including a

wash line 16, a sampling line 17, a waste aspirate line 18 and a media fill line 19. Also extending between the control unit 11 and each control head 38 and providing electrical communication therebetween is an electrical cable 21.

The control head 38 is shown in greater detail in Figs. 3-5. Retained by the control head 38 is a spray wash tube 39 connected to the spray wash line 16, a media fill tube 41 connected to the fill line 19, an aspiration probe 42 connected to the aspirate line 18, a sampling probe 43 connected to the sampling line 17, a pH adjustment and media replacement tube 44 connected to a pH adjustment and media replacement line 45 and a temperature detector 46. Also retained by the control head 38 is an aspiration probe drive mechanism 48, a sample probe drive mechanism 49 (Fig. 3), a stepping motor 51 (Fig. 4) and an interconnect board 52. Connected to the interconnect board 52 is a cable connector 53 that receives a plug 54 (Fig. 5) on the electrical cable 21. The head is covered by a cover 50.

A sample tablet dispenser 57 is mounted on the control head 38 and is coupled to the stepping motor 51. Attached to lower ends of the wash tube 39, the fill tube 41, the aspiration probe 42, the sampling probe 43 and the adjustment and replacement tubing 44, respectively, are a spray wash nozzle 63, an outwardly directed fill nozzle 61, an aspiration tip 62, a sampling tip 64 and an outwardly directed adjustment and replacement nozzle 65. A temperature sensing thermistor 66 of the temperature detector 46 is supported at a lower end of the sampling probe 43.

As shown in Fig. 5, the sampling probe drive mechanism 49 which is identical to the aspiration probe drive mechanism 48 includes a rack and gear drive 71 operatively coupled to the sampling probe 43, a servo motor 72, a position controlling potentiometer 73 and a gear box 74 coupling the servo motor 72 to the rack and gear drive 71. In response to appropriate energization of the servo motors 72, the rack and gear drives 71 produce reciprocating movement of the aspiration probe 42 and the sampling probe 43 into and out of the vessels 31.

The tablet dispenser 57 includes a receptacle 76 defining a plurality of circumferentially distributed stations 77, each for receiving a sample tablet to be dissolved in the liquid media 32 in the vessel 31. Rotatably supporting the receptacle 76 is a fixed plate 78 having an opening 79 aligned with a vertical passage 81 in the control head 38. The stepping motor 51 (Fig. 4) is mounted on a motor bracket 82 and is rotatably coupled to the receptacle 76 by a shaft 83 that also rotates a sensor disk 84. Also mounted on the motor bracket 82 is a photo detector 85 that senses the position of the

sensor disk 84 and thereby the rotational position of the receptacle 76. In response to appropriate energization of the stepping motor 51, the receptacle 76 is sequentially rotated into positions that produce sequential registration between each of the stations 77 and the opening 79. As each station 77 registers with the opening 79, a sample tablet is discharged through the passage 81 into the vessel 31. The photo detector 85 detects when an initially empty home station returns into registration with the opening 79 thereby indicating a need to reload the receptacle 76.

As shown in Fig. 6, the control unit 11 (Fig. 1) retains a wash manifold 91, a media tank 92 supported on a balance 93, a media pump 94, a pair of waste pumps 95, 96, a waste manifold 97 and a plurality of sampling filters 98 retained by the filter holding mechanism 14 (Fig. 1). The wash manifold 91 has inlets connected to an external hot water supply by a pair of parallel valves 101, 102 and a regulator 103; and a plurality of outlets each connected to a different one of the wash lines 16. Communicating with the media tank 92 and a helium sparge unit 104 therein through, respectively, valves 105, 106 are an external water source and a helium source. Dissolved gases in the liquid media within the tank 92 are eliminated by the sparge unit 104.

The media pump 94 has an inlet connected to the media tank 92 by a three-way valve 108 which also connects an external media tank 107 to the tank 92. An outlet of the media pump 94 is connected to a multiple port dispensing valve 109, outlets of which are connected to the media fill lines 19, the wash manifold 91 by a valve 111 and the waste manifold 97. Receiving the waste lines 18 are inlets of the waste pumps 95, 96, the outlets of which are connected to the waste manifold 97. The sampling lines 17 are connected to the inlets of the sampling pumps 13, the outlets of which communicate through the filters 98 with either an external six cell UV analyzer 115 or the inlets of a multiple port valve 116. Outlets of the valve 116 communicate either with the waste manifold 97 or an external valve 118 alternatively feeding either a UV analyzer 121, an HPLC system 122 or a fraction collector 123.

OPERATION

To initiate a test sequence, the media pump 94 is energized producing a flow of liquid media from the tank 92 through the valves 108 and 109, the fill lines 19, and the fill tubings 41 for discharge out of the nozzles 61 into the vessels 31. The amount of media flow is controlled by the balance 93 and the outward orientation of the nozzles 61 reduces splashing and air entrainment within the media

samples collected in the vessels 31. Next, the sampling probes 43 are moved downwardly into each of the vessels 31 allowing the thermistor sensors 66, to monitor the temperature of the liquid media 32 in each vessel. Once a desired temperature is obtained, the stepping motors 51 (Fig. 5) are either serially or simultaneously energized to produce registration of a filled station 77 of the receptacles 76 with the openings 79 in the plates 78 resulting in a release of a solid sample tablet into each of the vessels 31. During a dissolution period, the paddles 33 are activated to produce agitation of the liquid media 32 in each of the vessels 31.

To effect sampling during a given dissolution cycle, the sample probes 43 are lowered and the sampling pumps 13 are energized to withdraw a predetermined liquid sample from each of the vessels 31 through the sampling tips 64, the sampling tubes 42, the sampling lines 17 and the sampling filters 98 either individually into the six cell UV analyzer 115 or collectively into the valve 116 for discharge into one of the analyzer systems 121-123. Any excess media sample is discharged through a line 132 into the waste manifold 97. Once all desired sampling tests have been completed, the aspiration probe drive mechanisms 48 are activated to lower the aspiration probes 42 into the vessels 31. Energization of the waste pumps 95, 96 institutes aspiration of the vessels 31 through the aspiration tips 62 and the aspiration lines 18 into the waste manifold 97.

After all the vessels 31 have been emptied, the valves 101, 102 are opened to produce the flow of hot water through the wash manifold 91 and the wash lines 16 for discharge through the spray nozzles 63 to thoroughly clean the vessels 31. The expended cleaning liquid is discharged into the waste manifold 97 via the aspiration probes 42 and the aspiration lines 18 by the still energized waste pumps 95, 96. To prevent dilution of liquid media subsequently dispensed into the vessels 31 by any wash water remnant therein, the media pump 94 then is energized to produce media flow through an outlet of the valve 109 and the valve 111, the wash manifold 91 and the wash lines 16 and resulting in discharge of media through the spray nozzle 63. The sprayed media collects any water remnant therein and the combined liquid then is removed by the energized waste pumps 95, 96.

Also provided in the dissolution system is a pH adjustment and media replacement unit 141 shown in Fig. 6. Included in the unit 141 is a liquid handling syringe 142 and an air push syringe 143 connected by a 3-way valve 144. The output of the liquid syringe 142 is connected to a port of a multiple port valve 146 having outlet ports connected by the adjustment lines 45 to the media adjustment tubes 44 in the control leads 38. Facili-

tated by the unit 141 is either selective adjustment of the media pH in the vessels 31 or replacement of media that has been removed for sample testing so as to maintain a constant media volume within the vessels 31.

To initiate a media replacement operation, the valve 146 is moved into a position that provides communication between a fill line 148 and the liquid syringe 142. Next, the liquid syringe 142 is activated to accumulate a media charge of predetermined volume, and the air push syringe 143 is activated to accumulate a charge of air. After positioning of the valve 146 to connect the line 140 with an adjustment line 45 associated with a particular vessel 31, the liquid syringe 142 is activated to induce an appropriate flow of replacement media into the selected vessel 31 through the lines 140 and 45. Full delivery of the media replacement charge is provided by activation of the air syringe 143 to cause air flow through the valve 144, the liquid syringe 142 and the lines 140 and 45. Any excess material can be removed through a waste line 49 connected to the valve 146. The unit 141 can be used in the same manner to adjust the pH of the media content of the vessels 31. For pH adjustment, a suitable buffered solution is drawn into the liquid syringe 142 through the fill line 148 for ultimate discharge into the vessels 31.

Obviously, many modifications and variations of the present invention are possible in light of the above teachings. It is to be understood, therefore, that the invention can be practiced otherwise than as specifically described.

Claims

1. A dissolution testing system comprising:

base means;

a plurality of vessels mounted on said base means;

agitation means for agitating a liquid content of said vessels; and

head means supported above each of said plurality of vessels and comprising fill means operable to automatically inject a liquid media into said vessel.

2. A system according to claim 1 wherein said fill means comprises a fill nozzle disposed to inject the liquid media into said vessel and fill tubing providing communication between said fill nozzle and a source of liquid media.

3. A system according to claim 2 wherein said fill nozzle is disposed to direct the liquid media against a sidewall portion of said vessel.

4. A system according to claim 2 wherein said head means further comprises wash means for automatically introducing a cleaning liquid into said vessel.

5. A system according to claim 4 wherein said wash means comprises a spray nozzle disposed to spray the cleaning liquid into said vessel and wash tubing providing communication between said spray nozzle and a source of cleaning liquid.

6. A system according to claim 5 wherein said head means further comprises an adjustment means for automatically injecting a pH adjustment solution into said vessel.

7. A system according to claim 6 wherein said adjustment means comprises an adjustment nozzle disposed to inject the adjustment solution into said vessel.

8. A system according to claim 7 wherein said adjustment nozzle is disposed to direct the adjustment solution against a sidewall portion of said vessel.

9. A system according to claim 8 wherein said head means further comprises wash means for automatically introducing a cleaning liquid into said vessel.

10. A system according to claim 1 wherein said head means further comprises an adjustment means for automatically injecting a pH adjustment solution into said vessel.

11. A system according to claim 10 wherein said head means further comprises wash means for introducing a cleaning liquid into said vessel.

12. A system according to claim 1 wherein said head means further comprises sampling means for automatically withdrawing a liquid sample from said vessel.

13. A system according to claim 12 wherein said sampling means comprises a sampling probe for withdrawing the liquid sample and sampling drive means for moving said sampling probe into and out of said vessel.

14. A system according to claim 1 wherein said head means further comprises aspiration means for automatically removing the liquid content of said vessel.

15. A system according to claim 14 wherein said aspiration means comprises an aspiration probe for removing the liquid content and aspiration drive means for moving said aspiration probe into and out of said vessel. 5
16. A system according to claim 1 wherein said head means further comprises detector means for detecting the temperature of a liquid content of said vessel. 10
17. A system according to claim 16 wherein said detector means comprises a temperature sensor. 15
18. A system according to claim 1 wherein said head means further comprises dispenser means for automatically dispensing a solid sample into said vessel. 20
19. A system according to claim 18 wherein said head means further comprises sampling means for withdrawing a liquid sample from said vessel. 25
20. A system according to claim 19 wherein said head means further comprises detector means for detecting the temperature of a liquid content of said vessel. 30
21. A system according to claim 20 wherein said sampling means comprises a sampling probe for withdrawing the liquid sample and sampling drive means for moving said sampling probe into and out of said vessel. 35
22. A system according to claim 21 wherein said detector means comprises a temperature sensor mounted on said sampling probe. 40
23. A system according to claim 20 wherein said head means further comprises aspiration means for automatically removing the liquid content of said vessel. 45
24. A system according to claim 21 wherein said head means further comprises wash means for automatically introducing a cleaning liquid into said vessel. 50
25. A system according to claim 22 wherein said head means further comprises an adjustment means for automatically injecting a pH adjustment solution into said vessel. 55
26. A system according to claim 25 including a media source, and multiple port fill valve means connecting said media source to said fill means in each said head means.
27. A system according to claim 26 including analyzer means, and multiple port sample valve means connecting said analyzer means to said sampling means in each of said head means.
28. A system according to claim 27 including a cleaning liquid source connected to said spray nozzle in each of said head means.
29. A system according to claim 28 including a pH adjustment solution source and multiple port adjustment valve means connecting said solution source to said adjustment means in each of said head means.
30. A dissolution testing system comprising:
base means;
a plurality of vessels mounted on said base means;
agitation means for agitating a liquid content of said vessels; and
head means supported above each of said plurality of vessels and comprising sampling means for automatically withdrawing a liquid sample from said vessel.
31. A system according to claim 30 wherein said sampling means comprises a sampling probe for withdrawing the liquid sample and sampling drive means for moving said sampling probe into and out of said vessel.
32. A dissolution testing system comprising:
base means;
a plurality of vessels mounted on said base means;
agitation means for agitating a liquid content of said vessels; and
head means supported above each of said plurality of vessels and aspiration means for automatically removing the liquid content of said vessel.
33. A system according to claim 32 wherein said aspiration means comprises an aspiration probe for removing the liquid content and aspiration drive means for moving said aspiration probe into and out of said vessel.
34. A dissolution testing system comprising:
base means;
a plurality of vessels mounted on said base means;
agitation means for agitating a liquid content of said vessels; and
head means supported above each of said

plurality of vessels and comprising a temperature sensor for detecting the temperature of a liquid content of said vessel.

35. A system according to claim 34 wherein said head means further comprises sampling means for automatically withdrawing a liquid sample from said vessel. 5
36. A system according to claim 35 wherein said sampling means comprises a sampling probe for withdrawing the liquid sample and sampling drive means for moving said sampling probe into and out of said vessel. 10
37. A system according to claim 36 wherein said temperature sensor is mounted on said sampling probe. 15
38. A dissolution testing system comprising: 20
 base means;
 a plurality of vessels mounted on said base means;
 agitation means for agitating a liquid content of said vessels; and 25
 head means supported above each of said plurality of vessels and dispenser means for automatically dispensing a solid sample into said vessel.
39. A system according to claim 38 wherein said dispenser means comprises a receptacle for a plurality of solid samples, and release means for sequentially and selectively moving each of said solid samples into said vessel. 30
40. A method of dissolution testing in a system including a base means, a plurality of vessels mounted in situ on said base means, and agitation means for agitating a liquid content of said vessels; said method including the following steps: 40
 automatically filling each of said vessels in situ with a media liquid;
 automatically dispensing a solid sample 45
 into each of said vessels in situ;
 withdrawing liquid samples from each of said vessels in situ;
 simultaneously removing the liquid content of all said vessels in situ; and 50
 automatically washing each of said vessels in situ.
41. A method according to claim 40 wherein said liquid samples are sequentially withdrawn. 55
42. A method according to claim 40 wherein said liquid samples are simultaneously withdrawn.

43. A method according to claim 40 including the steps of sequentially injecting a pH adjustment solution into said vessels.

44. A method according to claim 40 including the steps of sequentially injecting doses of replacement liquid media into said vessels.

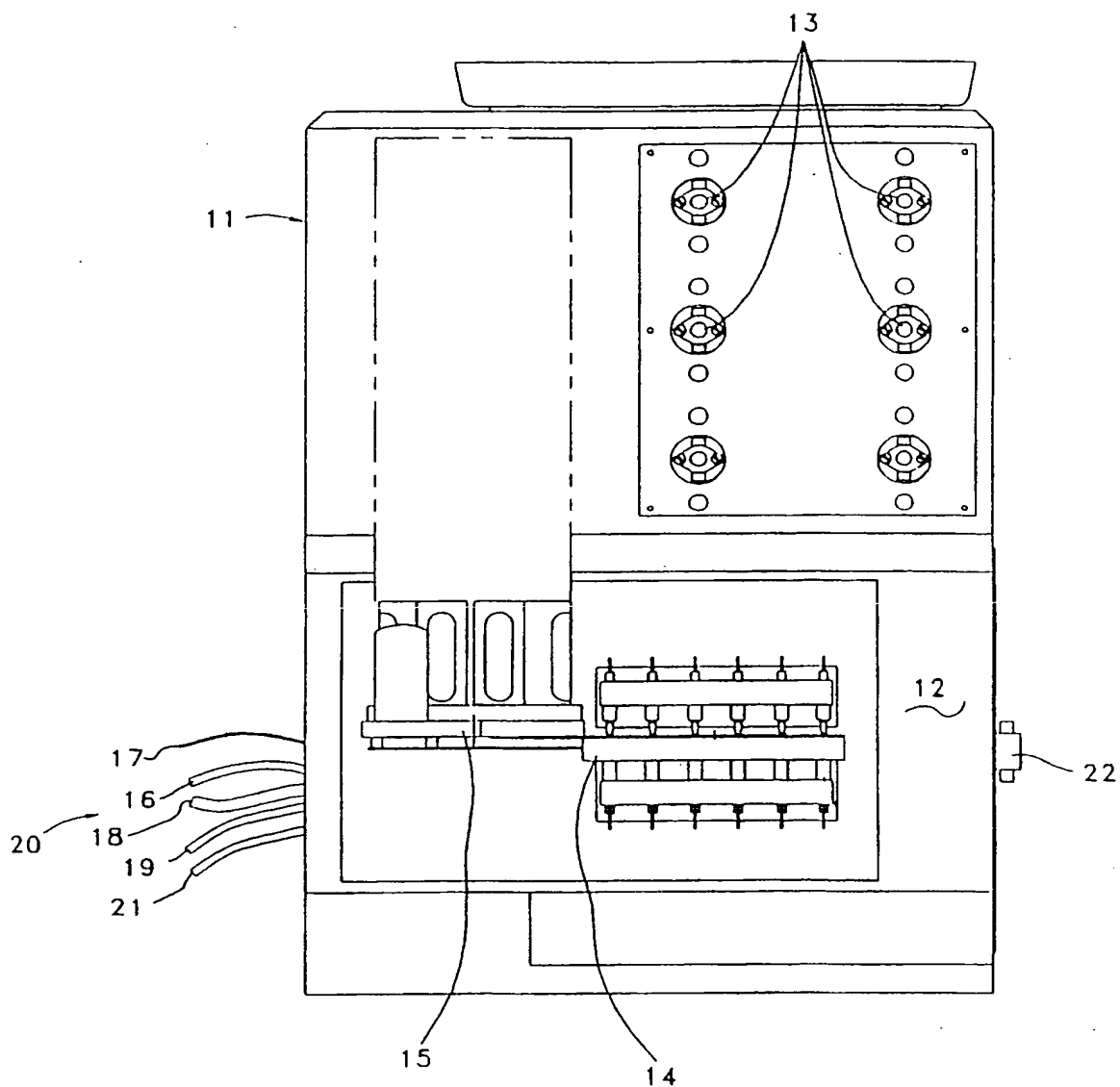


FIG. 1

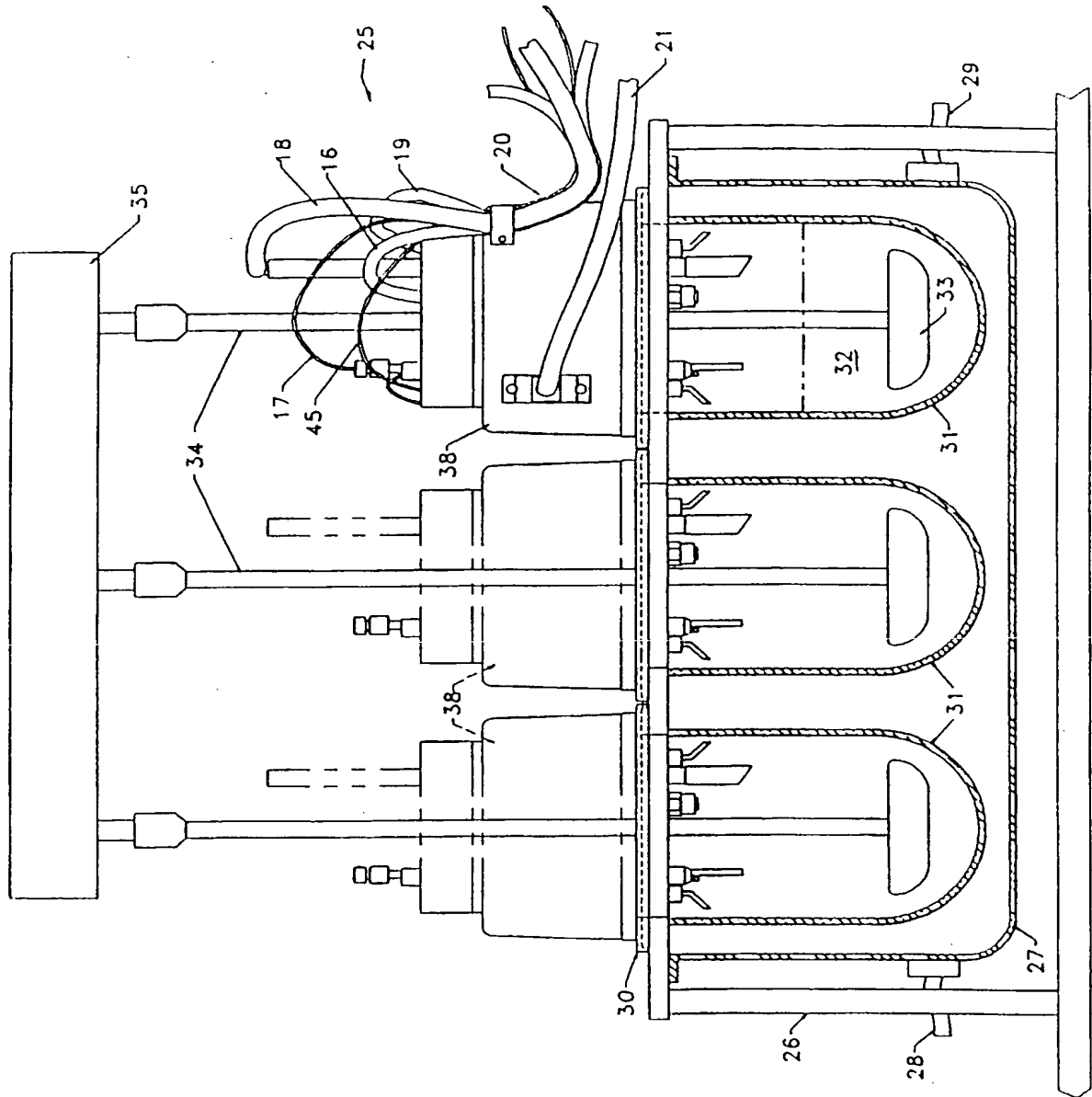


FIG. 2

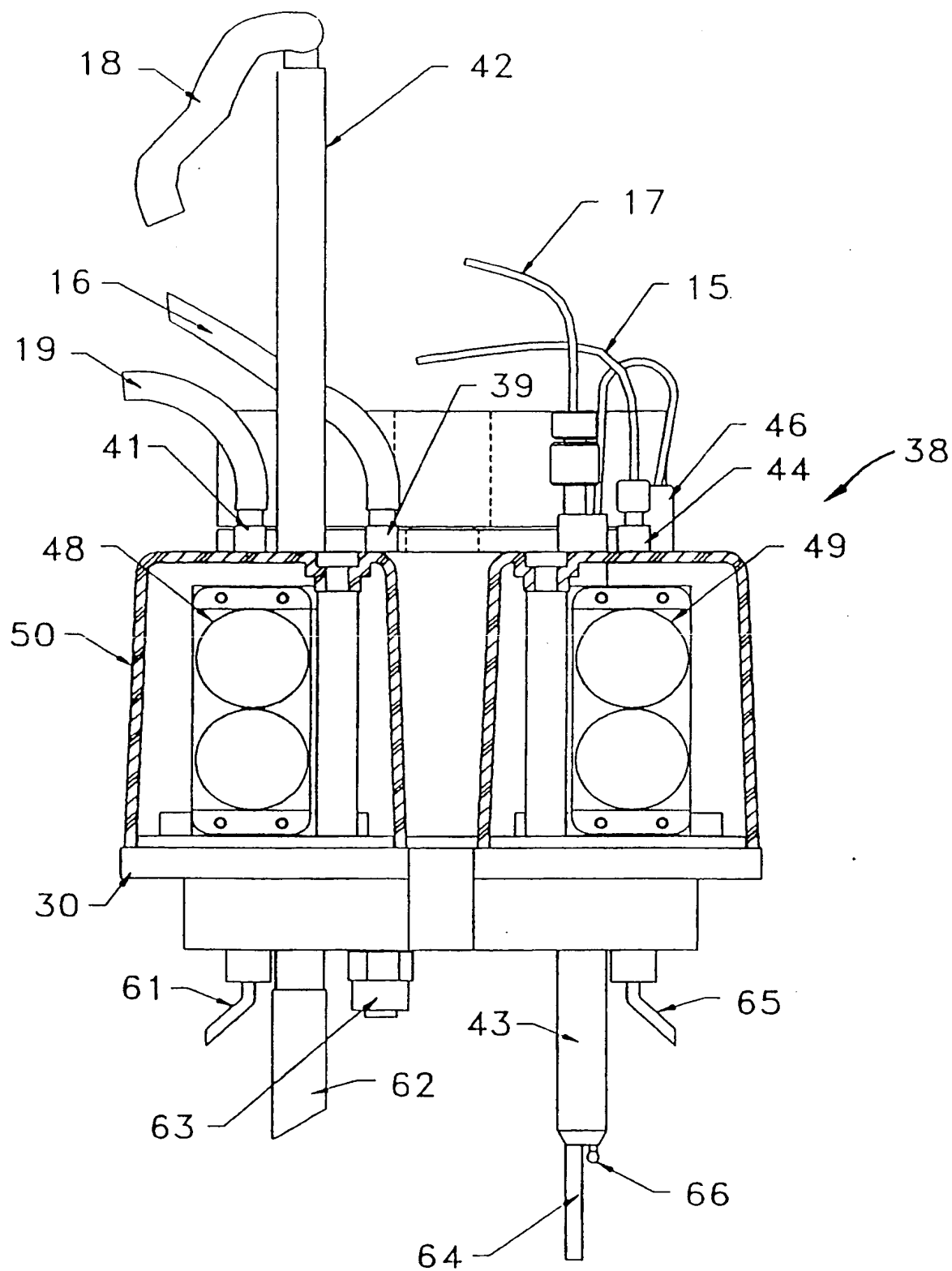


FIG. 3

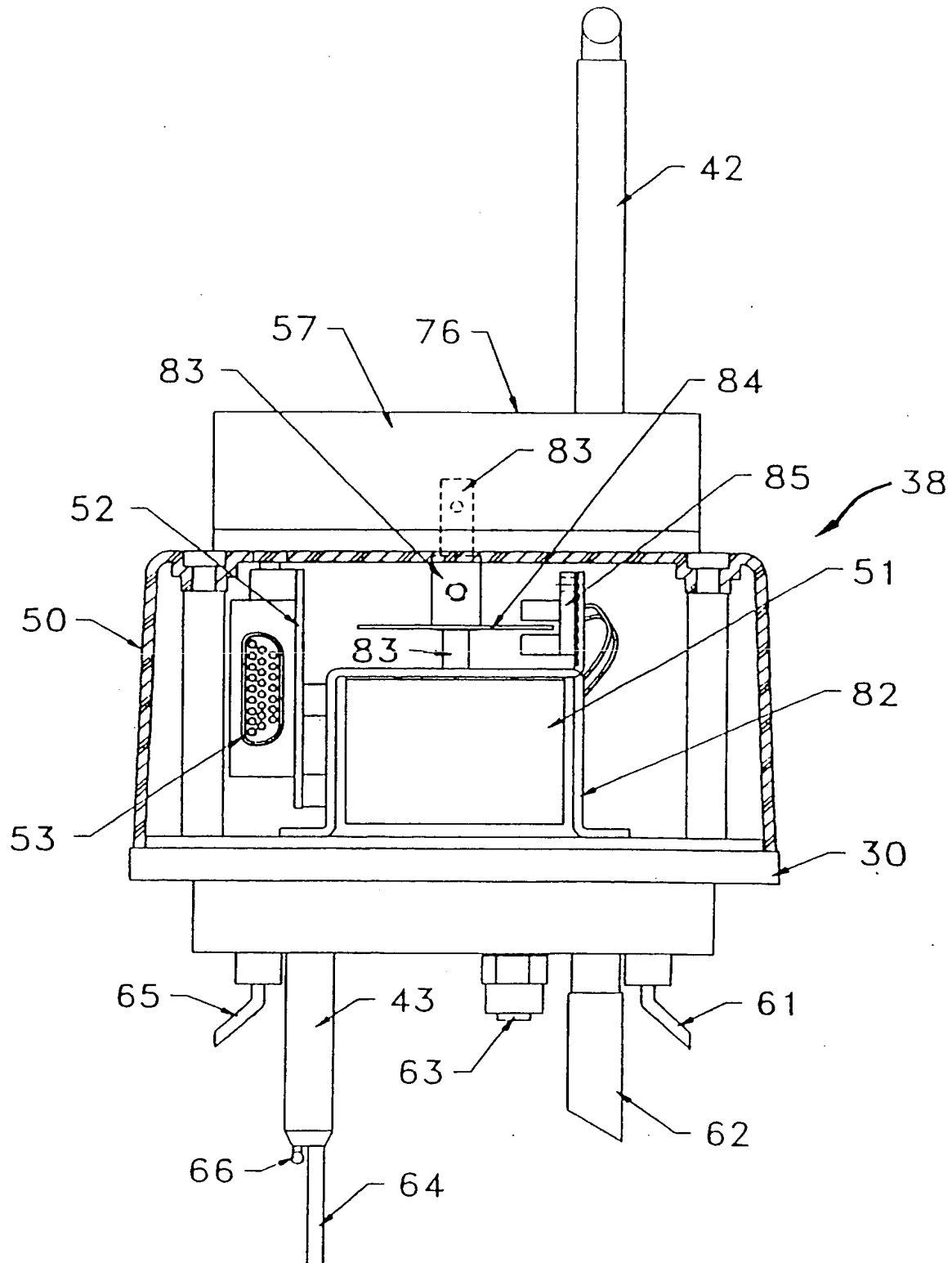


FIG. 4

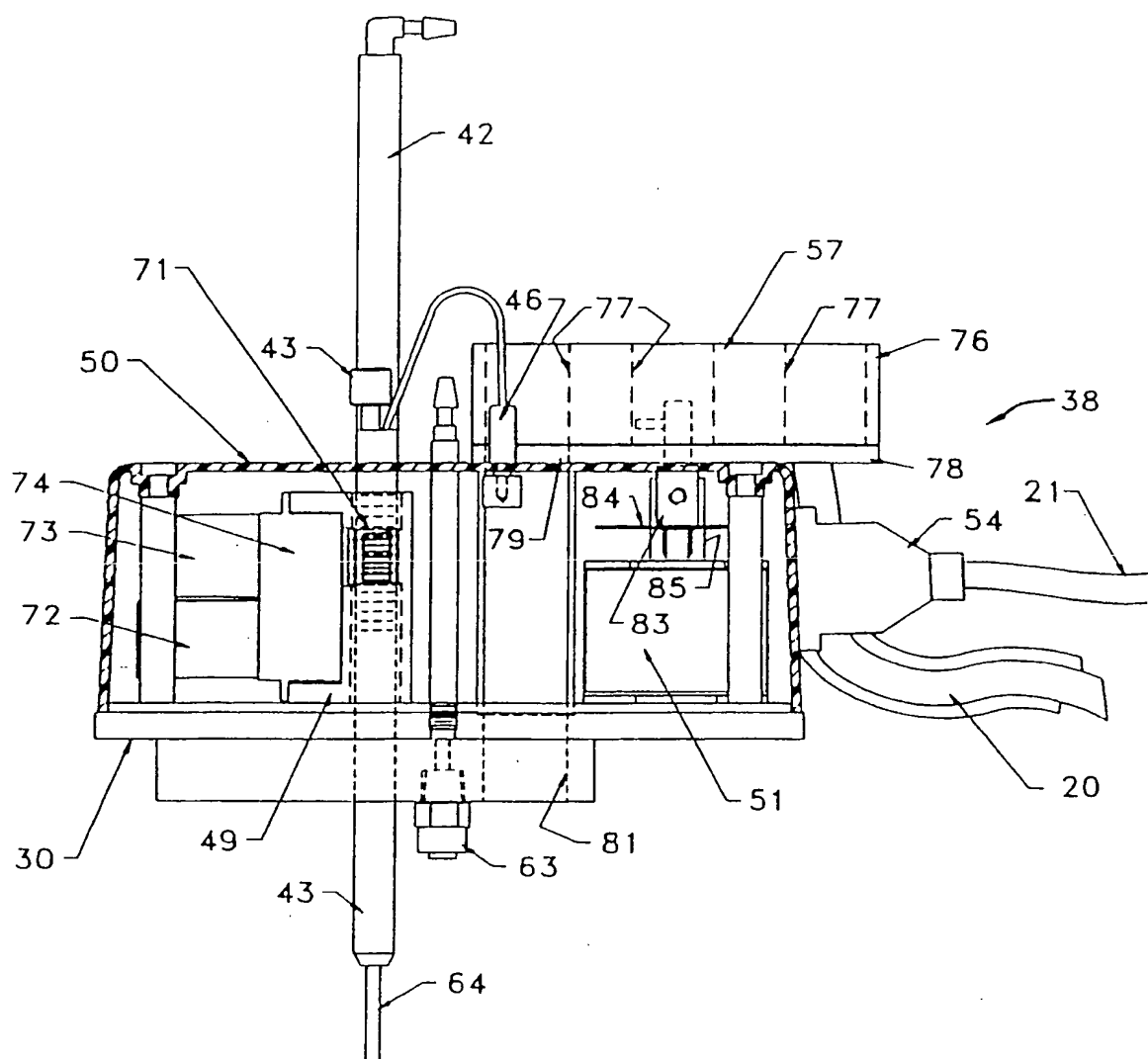
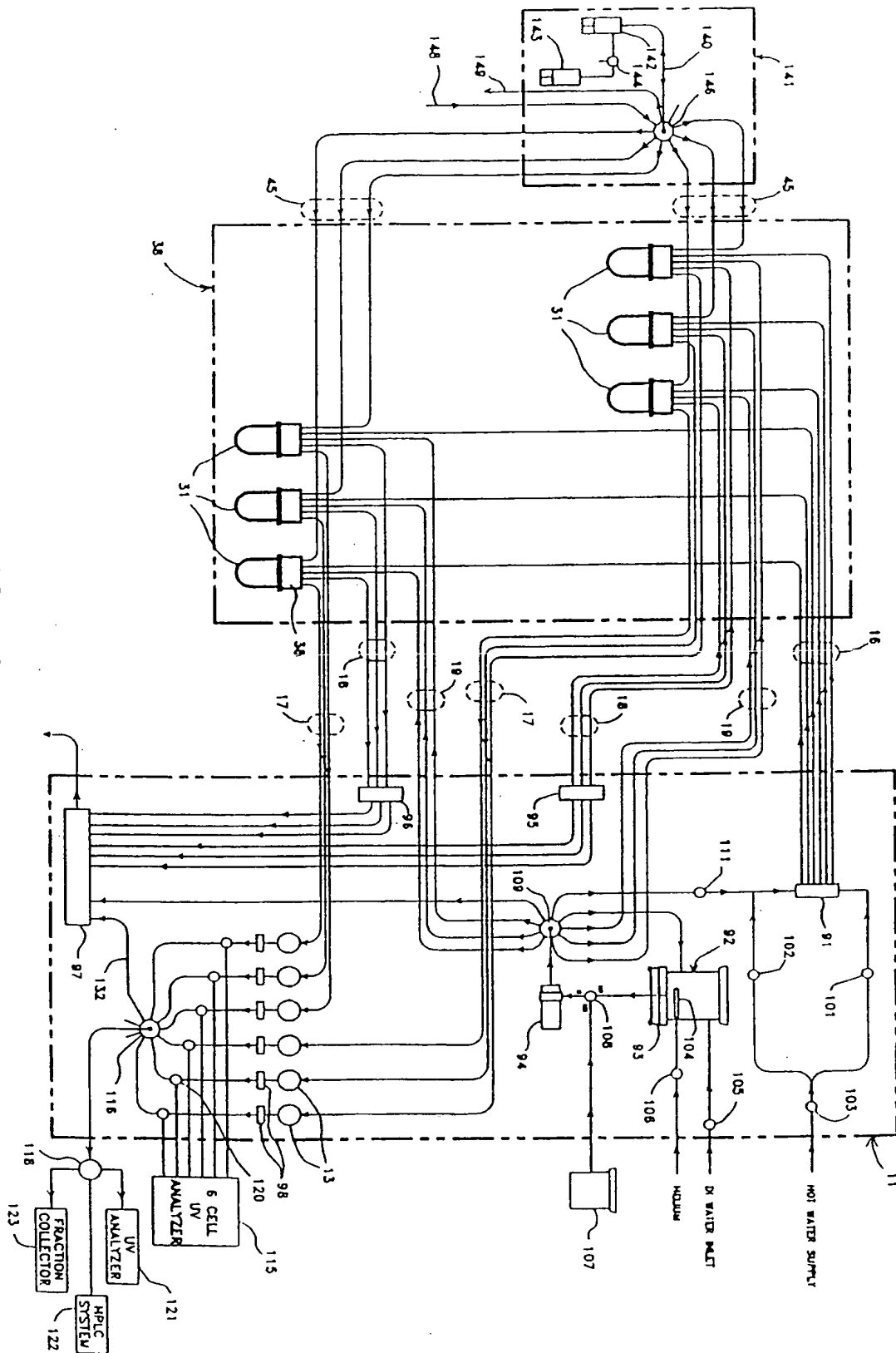


FIG. 5

FIG. 6





European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 94 30 5130

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 278 374 (PHARMATEST APPARATEBAU GMBH) 17 August 1988 * the whole document *	1-5, 12, 14, 16, 18, 30, 32, 34, 36, 38, 40	G01N13/00 G01N35/00 G01N33/15
A	WO-A-81 03072 (V. SMOLEN) 29 October 1981 * page 11, line 17 - page 12, line 5; figure 1 *	1-10, 40	
A	US-A-5 076 107 (J. TIMMERMANS ET AL.) 31 December 1991		
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			G01N
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 7 November 1994	Examiner Hodson, M
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document I : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☒ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,
namely claims: 12, 14, 16, 18, 30, 32, 34, 38 and 40
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.
namely claims:
- ☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims: